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Tri- and difluoromethoxylated *N*-based heterocycles – Synthesis and insecticidal activity of novel F_3CO- and F_2HCO-analogues of Imidacloprid and Thiacloprid

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ABSTRACT

The preparation of F_3CO- and F_2HCO-analogues of Imidacloprid and Thiacloprid and the evaluation of their biological activity have been performed. For this purpose, a first synthetic approach allowed the preparation of a desired F_3CO-containing key intermediate. To allow a facile access to the second F_2HCO-containing key intermediate, the difluoromethylation of hydroxylated *N*-based heterocycles has been developed using difluoromethyl triflate (a liquid non-ODS reagent) under air in aqueous conditions and with very short reaction time. The broad diversity of compatible heterocycles includes a large series of substituted hydroxy-pyridines, but also –pyrazoles, –pyrazine, –pyridazine, and –quinolines. The couplings of both key intermediates with the required 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine and [*N*(*Z*)]-*N*-2-thiazolidinylidene-cyanamide were successfully achieved using literature conditions. This work enables the preparation of valuable building blocks, which could lead to the discovery of new bioactive entities.

1. Introduction

Since some years ago, the electron-withdrawing trifluoromethoxy (F_3C-O) and difluoromethoxy (F_2HC-O) groups are becoming more and more important in modern crop protection but also in pharmaceutical chemistry [1–6], because they can protect an aromatic ring system against oxidative (or electrophilic) attacks. An increased stability towards degradation is observed for active ingredients or fragments containing this special substitution pattern. Based on its electronic properties, which are close to the halogen atoms chlorine and fluorine [7], the F_3C-O group has been referred as a super- [8] or a pseudo [9]-halogen. The fluorinated carbon adjacent to an oxygen atom increases lipophilicity as shown by the high value of the F_3C-O hydrophobic substituent parameter [10–12]. It appears that the F_3C-O substituent is far more lipophilic ($\pi = +1.04$) than the halogens and lies between a F_3C ($\pi = +0.88$) and a F_3C-S ($\pi = +1.44$) group. It may thus replace advantageously a fluorine atom ($\pi = +0.14$) in most molecules with the benefit of increased lipid solubility.

The trifluoromethoxy substituent can induce particular conformational changes due to its anisotropic character (in difference to the isotropic trifluoromethyl group) [13] and adopt an orthogonal orientation with respect to an arene plane, in contrast to the methoxy group, which normally lies in the plane of the arene [14,15]. In fact, the electron density of the non-bonding *p*-orbitals at oxygen is very low. The electrons of the oxygen *p*-orbital are delocalized into the antibonding orbitals of the trifluoromethyl C–F bonds [16]. As a consequence, the oxygen non-bonding orbitals are not conjugated with the aromatic ring system; therefore the F_3C-group of F_3C-O lies out of the arene plane, and the rotational barrier is significantly lower than that for a methoxy group [17–19]. This behaviour can be used to tune the binding affinity in drug-target complexes. The use of the F_3C-O-motif in pharmaceuticals led to major breakthroughs; Riluzole was the first drug approved for amylotropic lateral sclerosis treatment; Delamanid is included in the World Health Organization List for essential medicines as prodrug for tuberculosis treatment; Celikalim is a vasorelaxing agent protecting cardiac muscles. In addition, marketed agrochemicals bearing the F_3CO-motif display various possible MoAs; Indoxacarb is a Voltage-gated sodium channel (VgSoCh) blocker (stabilizes the

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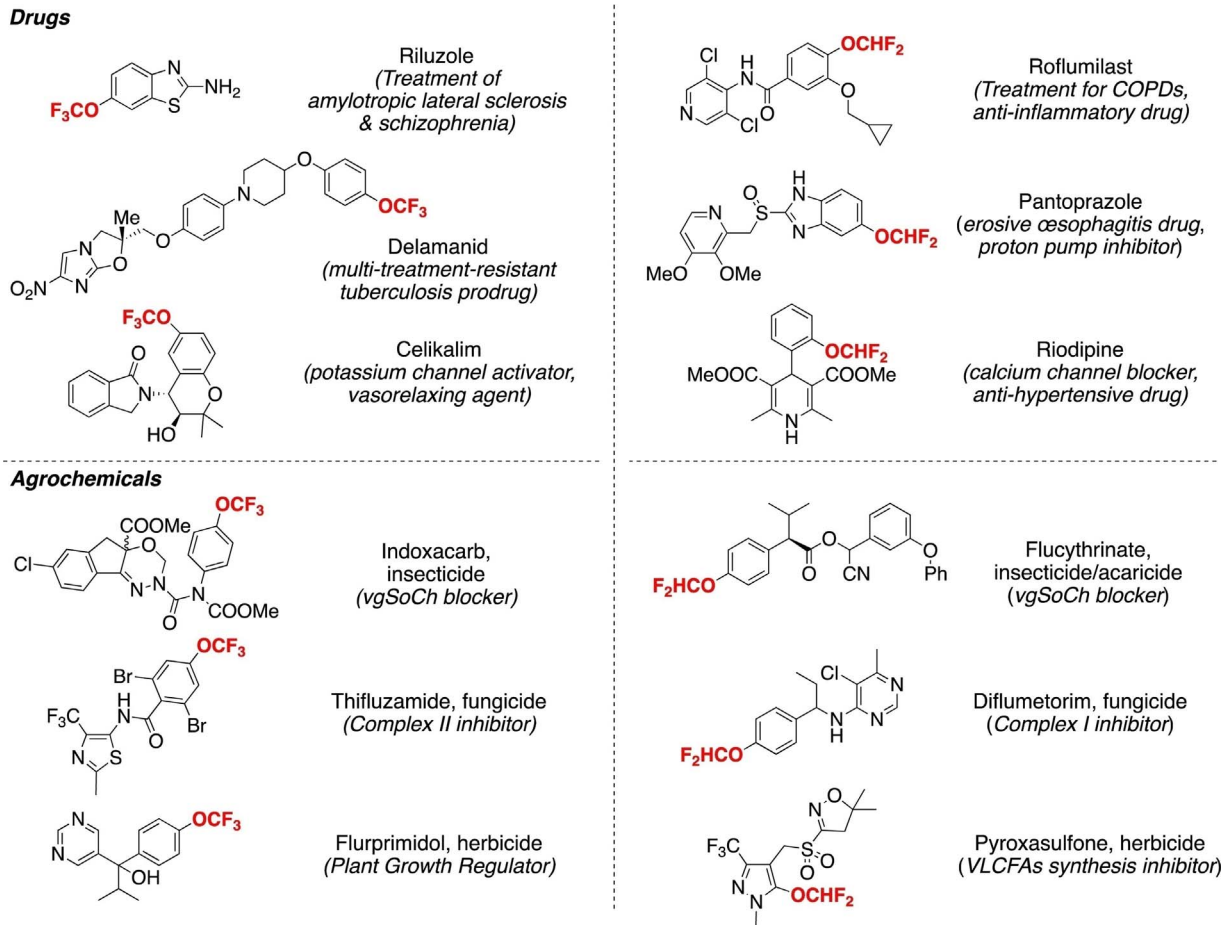

Fig. 1. F_3CO- and F_2HCO-bearing drugs and agrochemicals.

inactivated state); Thifluzamide is a fungicide (SDH Complex II inhibitor); Flurprimidol is a Plant Growth Regulator (or PGR) (Fig. 1).

The difluoromethoxy group shares several key properties with its renowned trifluoromethoxy analogue (high electronegativity, excellent lipophilicity, specific electronic distribution, thermal/chemical stability), but is not as bulky and displays an additional H-bonding capacity. This combination of properties makes the F_2CH-O-group more and more popular. It is found in medicinally relevant compounds that include enzyme inhibitors (*e.g.*: Roflumilast, a selective and long-acting phosphodiesterase-4 inhibitor, anti-HIV agents and antimicrobial agents). Pantoprazole is a nice example of F_2CH-O-containing drug found in the top 100 selling drugs in 2013, as well as several cardiovascular medications, such as Riodipine (Fig. 1) [1]. Surprisingly, most of marketed drugs are commonly bearing an aryl-$OCHF_2$ motif, but no example is known with heteroaryl-$OCHF_2$ motif.

Difluoromethoxy compounds are less described in marketed agrochemicals; only several examples containing a F_2CH-O-heteroaryl moiety are currently on the market: Diflumetorim is a fungicide (SDH Complex I inhibitor); Pyroxasulfone is a VLCFAs (Very Long Chain Fatty Acids) biosynthesis inhibitor; Flucythrinate, an insecticide acting as Voltage-gated sodium channel blocker, also contains this group (Fig. 1) [2].

These examples clearly illustrate the large potential of both F_3CO- and F_2HCO-substituents for the development of new bioactive ingredients. Therefore, we became interested in preparing new analogues of pyridine-containing neonicotinoid insecticides Imidacloprid and Thiacloprid, containing either 6-trifluoromethoxy- or 6-difluoromethoxy-pyridin-3-yl-methyl moieties.

2. Results and discussion

2.1. Trifluoromethoxy-derivatives

Our group was the first to report on the modular synthesis of a library of trifluoromethoxylated pyridines [17]. This approach has been applied in the synthesis of F_3CO-analogues of Imidacloprid and Thiacloprid.

According to our procedure, 2-chloro-6-hydroxypyridine was converted *in situ* into the corresponding chlorothionoformate and submitted to a chlorination with elemental chlorine in chloroform at room temperature yielding the corresponding trichloromethyl ether **1** in 60% yield (Scheme 1). Subsequent fluorination in the presence of antimony trifluoride and catalytic antimony pentachloride provided 2-chloro-6-trifluoromethoxypyridine **2** in 53% yield. Next, pyridine **2** was protected in the 3-position with a TMS group by metalation with lithium diisopropyl amide (LDA) and subsequent trapping with trimethylsilyl chloride (TMSCl). The nicotinic acid **4** was then prepared by metalation of **3** with lithium tetramethyl piperidide (LiTMP) followed by trapping with carbon dioxide and direct deprotection of the TMS group. Palladium-catalysed dechlorination to afford the 2-(trifluoromethoxy)nicotinic acid **5** was performed with 76% yield. The reduction of the acid into the corresponding primary alcohol was performed with 70% yield with BH_3·THF. The expected chlorinated product **7** was obtained by an *in situ* mesylation-chlorination in 56% yield. This product was further coupled with 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine or *N*-(4,5-dihydro-2-thiazolyl) cyanamide, to provide the two desired trifluoromethoxy analogues of Imidacloprid and Thiacloprid (**8** and **9**) in 38% and 74% yield respectively (Scheme 1).